

TET2 plays an essential role in erythropoiesis by regulating lineage-specific genes via DNA oxidative demethylation in a zebrafish model.

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Public Summary:

Although epigenetic modulation is critical for a variety of cellular activities, its role in erythropoiesis remains poorly understood. Ten-eleven translocation (TET) molecules participate in methylcytosine (5mC) hydroxylation, which results in DNA demethylation in several biological processes. In this research, the role of TETs in erythropoiesis was investigated by using the zebrafish model, where three TET homologs were identified. These homologs share conserved structural domains with their mammalian counterparts. Zebrafish TETs mediate the conversion of 5mC to hydroxymethylcytosine (5hmC) in zebrafish embryos, and the deletion of TET2 inhibits erythropoiesis by suppressing the expression of the *scl*, *gata-1*, and *cmyb* genes. TET2-upregulated lineage-specific genes and erythropoiesis are closely associated with the occurrence of 5hmC and demethylation in the intermediate CpG promoters (ICPs) of *scl*, *gata-1*, *cmyb*, which frequently occur at specific regions or CpG sites of these ICPs. Moreover, TET2 regulates the formation and differentiation of erythroid progenitors, and deletion of TET2 leads to erythrocyte dysplasia and anemia. Here, we preliminarily proved that TET2 plays an essential role in erythrocyte development by regulating lineage-specific genes via DNA oxidative demethylation. This report is anticipated to broaden current information on hematopoiesis and pathogenesis of hematopoiesis-related diseases.

Scientific Abstract:

Although epigenetic modulation is critical for a variety of cellular activities, its role in erythropoiesis remains poorly understood. Ten-eleven translocation (TET) molecules participate in methylcytosine (5mC) hydroxylation, which results in DNA demethylation in several biological processes. In this research, the role of TETs in erythropoiesis was investigated by using the zebrafish model, where three TET homologs were identified. These homologs share conserved structural domains with their mammalian counterparts. Zebrafish TETs mediate the conversion of 5mC to hydroxymethylcytosine (5hmC) in zebrafish embryos, and the deletion of TET2 inhibits erythropoiesis by suppressing the expression of the *scl*, *gata-1*, and *cmyb* genes. TET2-upregulated lineage-specific genes and erythropoiesis are closely associated with the occurrence of 5hmC and demethylation in the intermediate CpG promoters (ICPs) of *scl*, *gata-1*, *cmyb*, which frequently occur at specific regions or CpG sites of these ICPs. Moreover, TET2 regulates the formation and differentiation of erythroid progenitors, and deletion of TET2 leads to erythrocyte dysplasia and anemia. Here, we preliminarily proved that TET2 plays an essential role in erythrocyte development by regulating lineage-specific genes via DNA oxidative demethylation. This report is anticipated to broaden current information on hematopoiesis and pathogenesis of hematopoiesis-related diseases.

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